Resection of Gastrinomas

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Exploratory laparotomy and a search for gastrinomas was performed in 52 patients with the Zollinger-Ellison syndrome (ZES). Gastrinoma tissue was resected in 11 patients (21%), 6 (12%) of whom appear to have been cured. After surgery, serum gastrin levels in these six patients have remained normal from 10 months to 10 years. In the 46 other patients, tumor was unresectable because of metastases or multiple primary tumors (21 patients; 40%) or inability to find the tumor at laparotomy (21 patients; 40%). Multiple pancreatic islet cell adenomata were found in six of seven patients with multiple endocrine neoplasia (MEN), indicating that patients with this condition usually have diffuse involvement of the pancreas. The results of CT scans correlated with findings at laparotomy in 13 of 16 patients. The smallest tumor detected by CT scans was 1 cm in diameter. CT technology is more accurate in finding gastrinomas now than in the past and has a useful role in preoperative evaluation. The possibility of resection should be seriously considered in every patient with Zollinger-Ellison syndrome. Abdominal CT scans, transhepatic portal venous sampling, and laparotomy should be used to find the tumor and to determine whether it is resectable. Using presently available methods, it should be possible to cure about 25% of patients with gastrinomas who do not have MEN and over 70% of those without MEN who appear to have a solitary tumor. Total pancreatectomy may be necessary to cure some patients with MEN, but that operation is rarely justified. The morbidity and mortality of surgical attempts at curing this disease have become minimal; we have had no deaths or serious complications following such operations in over 10 yrs. Total gastrectomy and indefinite use of H_2-receptor blocking agents are the therapeutic options for patients with unresectable gastrinomas. Because H_2-receptor blocking agents fail to control acid secretion in many patients after several yrs of therapy, total gastrectomy is indicated in a large proportion of patients whose tumors cannot be resected. Total gastrectomy in patients with ZES is also safe using current techniques; our last death following this operation for ZES occurred 15 yrs ago.

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GASTRIN-SECRETING TUMORS (gastrinomas) often cannot be completely removed because of their location, multiplicity, or malignancy, and in the past, total gastrectomy was the preferred treatment for most patients with the Zollinger-Ellison syndrome. Total gastrectomy removes the source of the acid that causes ulcer disease, and the short and long-term results are excellent. In recent years, however, indefinite use of H_2-receptor blocking agents has been recommended as primary therapy. The short-term results have been good, but over the long run, acid secretion eventually escapes from the control of these drugs in most patients.[1]

It has always been appreciated that complete resection of gastrinomas would be optimal therapy, but until gastric acid secretion could be effectively suppressed, many patients with the Zollinger-Ellison syndrome came to surgery when they had fulminant ulcer disease.[7] Attempts at resection were sometimes unsuccessful, and patients with an incomplete resection were prone to serious postoperative complications from persistent ulcer disease.

H_2-receptor blocking agents have largely solved the problem of perioperative control, and more aggressive attempts at tumor resection have become safe. Sufficient experience has now accumulated to reassess the role of tumor resection for Zollinger-Ellison syndrome. The results indicate that tumor resection has a significant chance of curing the patient, and because it obviates potential long-term problems, resection should be seriously considered in every patient.

Material and Methods

Since 1960, 52 patients with Zollinger-Ellison syndrome had laparotomy and exploration for tumor. One patient who had only peritoneoscopy with biopsy of a hepatic metastasis is included. Any patient who had a total gastrectomy without a search for tumor was excluded. There were 27 men and 25 women whose ages ranged from 15 to 67 yrs. Fifteen (29%) patients had MEN I, manifested by hyperparathyroidism in all patients, a familial history of ulcer disease in 10 patients, and other endocrine tumors in 10 patients.

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Of the 21 patients in whom no tumor was found, the diagnosis of Zollinger-Ellison syndrome was made before surgery by finding both hyperacidity and hypergastrinemia. The majority of these patients also had positive secretin or calcium tests. The gastrin values ranged from 200 to 15,000 pg per ml (normal < 100 pg/ml). Secretin tests were performed and were positive in all patients with basal gastrin levels below 500 pg/ml. Basal acid secretion ranged from 25 to 50 meq H+/hr in previously unoperated patients and 2 to 20 meq H+/hr in patients with one or more previous ulcer operations. These patients had a 1 to 20-yr history of ulcer symptoms (median 3 yrs).

Thirty-one patients with histologically proven islet cell tumors had basal acid secretion of 30 to 110 meq H+ per hour in unoperated patients and 4 to 20 meq H+/hr in patients with previous ulcer operations. Basal gastrin values ranged from 145 to 14,000 pg/ml. Secretin tests were positive in all patients whose basal gastrin levels were below 500 pg/ml. The history of ulcer disease was from 1 to 20 yrs (median 6 yrs).

Gastric analysis was performed after an overnight fast. A nasogastric tube was placed in the stomach and 4 consecutive 15 min specimens were collected. To calculate the acid concentration, an aliquot of each specimen was titrated to neutrality using an autotitrator, and H+ concentration was multiplied by volume of the specimen to determine total H+ content. Hourly acid output was expressed as the sum of four consecutive 15 min specimens.

Serum gastrin was measured by radioimmunoassay as described previously.[2] Methods of performing and interpreting the secretin and calcium tests have been previously reported.[3]

Patients whose tumors were resected were monitored after surgery with frequent gastrin determinations. Absence of ulcer disease, normal gastrin values, and lack of a response to secretin were all required to conclude that resection of the tumor was complete. If resection was unsuccessful, further medical or surgical therapy was instituted. If gastrin levels remained normal basally and after secretin stimulation, no further therapy was given, and the patient was followed at least yearly with serum gastrin measurements.

In an attempt to localize tumor before surgery, all patients diagnosed as having gastrinoma in the past 4 yrs have had abdominal CT scans performed with a GE 8800 scanner. After examination of the upper abdomen using 1 cm sections, the pancreas was re-examined using 5 mm sections. During rapid sequence pancreatic scanning, 50 to 100 ml of 60% meglumine diatrizoate was administered as an intravenous bolus. A total of 15 to 25 5 mm sections were obtained at the level of the pancreatic head, body, and tail. The scans were evaluated for abnormalities in contour of the pancreas and appearance of a vascular blush following administration of the contrast material.

Results

Since 1960, 52 patients with Zollinger-Ellison syndrome underwent laparotomy. No tumor was found in 21 patients, all but one of whom were treated by total gastrectomy. There were two postoperative deaths, one after total gastrectomy and one after subtotal gastrectomy. Autopsies in these two patients revealed a solitary 8 mm submucosal duodenal tumor in one patient and multiple pancreatic adenomata in the second patient, who also had multiple endocrine neoplasia (MEN).

Tumor was found in 31 (60%) patients, 12 of whom had MEN. Resection for cure was attempted in 11 (21%) of these patients and was successful in 6 (12%). Of the 19 patients who had demonstrable tumor and who did not have MEN, resection was successful in 5 (26%) and was unsuccessful in 2. Thus, among the seven patients without MEN in whom curative resection was attempted, the operation was successful in 5 (71%). These patients are described in Table 1. After successful resection, serum gastrin levels fell to normal within 24 hrs of operation and have remained there from 10 mths to 10 yrs. Fig. 1 depicts the changes in serum gastrin levels and gastric acid secretion after complete resection of a gastrinoma. In three patients with intact stomachs who were cured, basal gastric acid secretion fell below 10 meq H+/hr.

Resection was accomplished by distal pancreatectomy or enucleation of a tumor in the pancreatic head in all but one patient. The only patient (no 1) with MEN who was cured had a total pancreatectomy for insulinomas and gastrinomas. Both the hyperinsulinemia and hypergastrinemia resolved. Patient no 6 had a left hepatic lobectomy for a solitary metastasis and a distal pancreatectomy for a solitary pancreatic gastrinoma.

Tumor resection was unsuccessful in four patients and was of uncertain success in one patient. The operation was performed in 1966 in one of these patients (no 7), before gastrin assays were available, and the patient died after surgery. Two patients with MEN (no 9 and no 10) underwent distal pancreatectomies that included all grossly evident tumor. Both specimens contained multiple adenomata, and hypergastrinemia persisted in both patients after surgery. Patient no 8 had resection of three tumors in the head of the pancreas, but gastrin levels remained elevated. These last three patients have subsequently had total gastrectomy for control of the disease.

Patient no 11, in whom the results of resection are equivocal, had two tumors enucleated from the head of the pancreas. She became asymptomatic after surgery, and her gastrin concentrations decreased, but they re-

TABLE 1A. *Patients Cured by Resection*

Patient	Age	Sex	Men	Pathologic Findings	Procedure	Year	Gastrin pg/ml Pre	Gastrin pg/ml Post	Follow-up
1	30	F	Yes	Insulinoma, gastrinoma; multiple pancreatic tumors	Total pancreatectomy	1973	2600	20	10 yrs; normal gastrins, 1982
2	37	M	No	2 cm tumor in tail of pancreas	Distal pancreatectomy	1975	500	12	8 yrs; normals gastrins, 1982
3	65	F	No	1 cm tumor in tail of pancreas	Distal pancreatectomy, total gastrectomy	1975	2000	24	1 yr; died of other causes, 1976
4	56	F	No	6 cm tumor in body of pancreas	Distal pancreatectomy	1978	241	16	4 yrs; normal gastrins, 1982
5	54	M	No	2 tumors: 7 cm in head of pancreas, 1 cm in duodenum	Tumor enucleation, total gastrectomy	1979	2000	76	3 yrs; normal gastrins, 1982
6	56	F	No	1 cm tumor in tail of pancreas; 3 cm metastasis, L lobe of liver	Distal pancreatectomy, left hepatic segmentectomy	1982	1400	10	10 mo; normal gastrins, 1983

The 5 surviving patients are all asymptomatic.

main in the 100 to 300 pg/ml range, above normal in our assay.

CT scans were performed in 16 patients who had laparotomies, and they were accurate in 13 (81%) patients. The scan accurately localized tumors in the pancreas in seven of ten patients with tumor found at surgery. There were three false negative scans, all for tumors 1 cm or less in diameter. In one of these patients, a 1 cm pancreatic tumor was found in an area different from that thought to be abnormal by preoperative CT scans. In six patients with no tumor found at surgery, the preoperative CT scans were negative. The CT scans were 100% accurate in demonstrating hepatic metastases in 4 of the 16 patients.

TABLE 1B. *Patients Not Cured by Resection*

Patient	Age	Sex	Men	Pathologic Findings	Procedure	Year	Gastrin pg/ml Pre	Gastrin pg/ml Post	Follow-up
7	50	F	Yes	4 × 5 cm tumor in head of pancreas (islet cell carcinoma)	Tumor resection; subtotal gastrectomy	1966			Died postop of perforated ulcer; resection incomplete on autopsy.
8	67	M	No	Three 1-2 cm tumors in head of pancreas	Tumor resection	1979	>1000	<1000	Cimetidine therapy unsuccessful; total gastrectomy. Alive and well.
9	31	M	Yes	Nodular pancreas; multiple islet cell tumors, staining for both gastrin and insulin	Distal pancreatectomy; parietal cell vagotomy	1979	556	2920	Cimetidine therapy unsuccesful; total gastrectomy. Alive and well.
10	58	F	Yes	Nodular pancreas; multiple islet cell tumors, staining for gastrin and insulin	Distal pancreatectomy performed for insulinoma	1980	6000	>2000	Total gastrectomy before pancreatic resection. She is alive and well with normal insulin levels.
11*	32	F	No	Two nodules in head of pancreas	Enucleation of two tumors in head of pancreas; parietal cell vagotomy	1980	250	150	Alive and well, 2 yrs; no further treatment.

* The gastrin levels have remained mildly elevated in this patient, and we suspect that she has had an incomplete resection, although she is asymptomatic and has a negative secretin test.

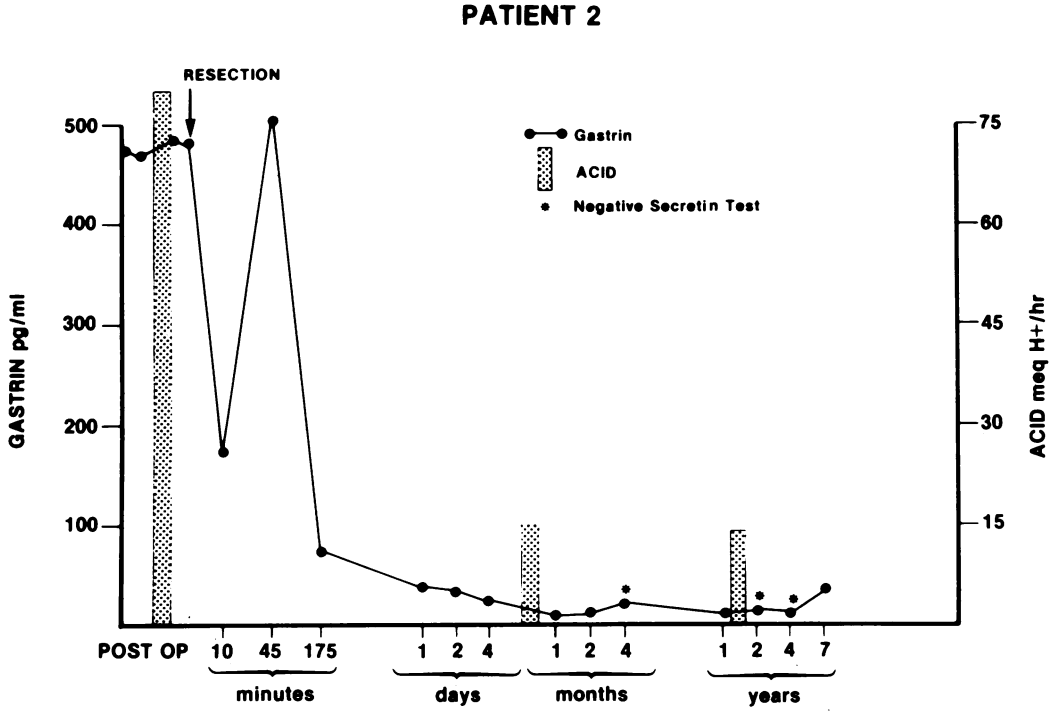

FIG. 1. Gastrin levels and gastric acid secretion following successful resection of a gastrinoma in patient no 2.

Of 20 patients with tumor who did not undergo resection, the lesions in 13 patients were judged to be unresectable, and 3 patients had multiple pancreatic tumors. In the remaining four patients, whose operations were performed before H_2 blocking agents were available, the surgeon was unwilling to risk incomplete resection. Table 2 outlines the reasons for not resecting tumor. Sixteen patients were treated with total gastrectomy, and there were no operative deaths. The remaining six patients had lesser ulcer operations before H_2 blocking agents were available, and they all died after surgery of ulcer complications.

We were unable to cure hypergastrinemia by partial pancreatectomy in 3 patients with MEN. Of seven MEN patients who had biopsy or resection of pancreas, six had multiple small islet cell tumors involving the entire specimen and one had islet cell carcinoma, suggesting that patients with this condition usually have involvement of the entire gland. The only MEN patient in whom resection removed all gastrinoma had a total pancreatectomy (Table 3).

In summary, resection was successful in 6 (12%) of 52 patients who underwent laparotomy for Zollinger-Ellison syndrome. There have been no postoperative deaths from attempts at tumor resection for over 15 yrs; the only such death (17 yrs ago) could have been prevented by cimetidine. Total gastrectomy was performed in 40 patients to control ulcer disease, with one (3%) operative death.

No deaths have occurred as a result of surgery for Zollinger-Ellison syndrome for 13 yrs, a period during which 38 patients have undergone a total of 45 operations.

TABLE 2. *Principle Reason for Not Resecting Tumor during Laparotomy*

	No. patients
1. Metastases to the liver or transverse mesocolon	11
2. Multiple pancreatic tumors	3
3. Before cimetidine (surgeon not willing to risk resection as treatment)*	4
4. Infiltrating tumor head of pancreas; would require a pancreaticoduodenectomy	2
	20

* These four patients were potentially resectable, but they had total gastrectomy instead.

Discussion

For many years the preferred treatment of the Zollinger-Ellison syndrome was total gastrectomy.[3-5] Tumor resection was possible in only a few patients, and the risk of ulcer-related complications in patients with incomplete resections was prohibitively high.[6-8] Nevertheless, sporadic reports of successful resection, par-

TABLE 3. *Histopathology in Patients with MEN*

	No. Patients
Multiple tumors	6
Carcinoma	1
	7

ticularly of duodenal tumors, appeared in the literature.[9-14] Recently, complete resection of a large gastrinoma in the head of the pancreas has been reported.[15]

H_2-receptor blocking agents have made attempts to resect tumor safer and more reasonable because they control the gastric acid hypersecretion and allow a more leisurely preoperative workup.[17,18] They also control gastric acidity after surgery until it can be determined whether or not resection has been successful.

Postoperative gastrin measurements are the main determinant of success or failure. In our experience, a fall of serum gastrin to normal in the immediate postoperative period has always correlated with a permanently successful resection. However, others have described patients whose serum gastrin levels fell initially and then gradually increased over months or years.[13,18] If the gastrin values become normal after tumor resection, we discontinue antacids and H_2-receptor blocking agents and follow the patient with monthly gastrin measurements for 1 year and with semiannual measurements thereafter. Although its value is still unproved, secretin testing probably increases the sensitivity of detecting tumor recurrence, and we have performed secretin tests in all patients whom we thought were cured.

Most patients with MEN are poor candidates for resection. The gastrin source has been reported to be diffuse within the pancreas by transhepatic portal venous sampling in patients with MEN I, and we had a similar result in one such patient we studied.[18] Six of our seven MEN patients had multiple pancreatic tumors, which suggests that total pancreatectomy would usually be required to cure these patients. In general, however, the morbidity of total pancreatectomy is greater than the combined risks of total gastrectomy and death from tumor, and total pancreatectomy is rarely indicated. The successful total pancreatectomy performed in one of our patients with MEN was done principally for refractory hyperinsulinism.

The reason for not resecting tumor in about 30% of patients has been inability to locate the lesion before surgery (using conventional studies, such as arteriography and CT scans) or at laparotomy. Transhepatic sampling of portal venous blood for gastrin levels may reveal the location of the tumor if a difference in hormone levels is detected between sampling sites.[18-20] Burcharth et al., who used transhepatic portal venous sampling in 11 patients, found gradients in eight patients, four of whom had successful resections. One patient had a hepatic metastasis, and one patient had resection of normal tissue.[19] Roche et al. reported correctly localizing gastrinomas in 15 of 16 patients using portal venous sampling.[20] Seven of these patients had no gross tumor seen at laparotomy, and tumor presence was confirmed by biopsy of the area indicated by portal venous sampling. Therefore, this method may be useful before surgery to localize gastrinomas, and it may allow tumor resection to be performed in patients whose tumors could not otherwise be found by direct inspection at laparotomy.

CT scanning has been helpful in localizing gastrinomas larger than 1 cm in diameter.[21-23] Of 16 patients proved at laparotomy to have gastrinomas who also had CT scans, 8 had pancreatic lesions detected. These were in the predicted site in seven patients, and one was a false-positive scan. CT scans correctly identified hepatic metastases in four patients. The smallest hepatic tumor seen was 1 cm in diameter. The CT scan failed to detect several 5 mm peritoneal implants and two tumors 1 cm in diameter in three patients. Of eight patients with negative pancreatic scans, two patients had multiple 1 to 7 mm pancreatic tumors. The other patients had no tumors found at laparotomy. Although the utility of the CT scan is limited by its power of resolution, it is now a valuable means of finding tumors in the pancreas and liver, and with improvements in equipment, its accuracy should continue to increase. Our current diagnostic strategy is to perform CT scans first, and to reserve transhepatic portal venous sampling for patients with a negative or equivocal CT scan.

In deciding which patients with gastrinoma are candidates for resection, one should compare the morbidity of resection with that of total gastrectomy or medical management with H_2-receptor blocking agents. Patients with isolated lesions of the body or tail of the pancreas that can be removed by distal pancreatectomy, and patients with tumors of the duodenal wall and head of the pancreas that can be enucleated are surely candidates. These operations are associated with less morbidity than total gastrectomy, and if they would remove all gross tumor, they are preferable as the initial procedure. Solitary tumors in the head of the pancreas may be removed by enucleation.[16,20] If enucleation is impossible, we are reluctant to perform a pancreaticoduodenectomy for gastrinoma unless the chances of curing the patient are unquestionably high.[16,20] The mortality and morbidity of pancreaticoduodenectomy is greater than that of total gastrectomy, and if the operation leaves residual gastrinoma, the patient may still require a total gastrectomy.

Presently, we treat all patients newly diagnosed as having gastrinomas with cimetidine and try to determine the extent of tumor. If preoperative tests demonstrate a primary tumor with or without hepatic metastases, we perform a laparotomy and determine if the primary lesion is resectable by distal pancreatectomy or enucleation. If there is no tumor demonstrated after surgery, we still recommend an exploratory laparotomy.

If no tumor is found or if the tumor is not resectable and preoperative control with H_2-receptor blocking agents has been good, we perform a parietal cell vagotomy and continue drug therapy after surgery. If preoperative control with H_2-receptor blocking agents has

been less than ideal, or if the dose of cimetidine required to keep H+ output below 10 mEq/hr exceeds 4.8 g/day, total gastrectomy is performed.[1,2]

As demonstrated by one of our patients, hepatic metastases are not a contraindication to curative surgery. The only requirement for curative surgery is that all gross tumor be resectable, which includes secondary tumors as well as the primary. The long-term success of resection in patients with metastatic disease is yet to be determined, but a strategy similar to that used in our patient is currently being used with some success for adenocarcinoma of the colon, and the rationale appears to be sound.

Conclusions

This experience supports the following conclusions: (1) gastrinoma involves the entire pancreas in most patients with MEN; (2) total pancreatectomy may be necessary to cure the Zollinger-Ellison syndrome in MEN, although this procedure would be rarely indicated; (3) CT scans can often find gastrinomas; (4) it is possible to cure some patients with hepatic metastases; (5) tumors of the head of the gland may be cured by enucleation; (6) the morbidity of operations aimed at removing all gastrinoma is now very low; (7) resection of all visible gastrinoma in patients without MEN has about a 70% chance of curing the patient; (8) overall, it should be possible to cure more than 25% of patients with gastrinoma who do not have MEN; (9) the quality of life after successful resection of a gastrinoma is so much better than with other forms of therapy that the possibility of resection should be aggressively pursued in every patient.

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Discussion

Dr. Murray F. Brennan (New York, New York): A year ago, we presented data at this meeting on 33 patients whom we had managed over a 6-year period with a conservative approach, and ended by arguing, much as the present group has, for staging laparotomy. I believe this data would support that approach most affirmatively.

My recent experience in New York City has been with the much more advanced cases, and that has only served to reinforce the need for early, aggressive surgery, rather than watching these people suffer with ineffective multimodality therapy for advanced disease.

The central issue, though, is the localization in those patients in whom the tumor is not readily identified, or will not be readily identified. The arteriogram has been surprisingly useless for gastrinoma, in contradistinction to insulinoma, serving only to identify the vascular hepatic metastases.

The CT scan, as the present authors have shown, is good, but it identifies lesions of 1 cm or greater. Selective venous sampling does have a role. Two of our recent six patients have been identified with selective venous sampling to have tumors in a localized area, not identifiable at the time of surgery. I noticed in the summary they mentioned the use of selective venous sampling. I hope you will comment as to its appropriateness.

I would like to disagree with only one feature, and that is the decision not to operate on people with multiple endocrine neoplasia. The problem with multiple endocrine neoplasia is not so much the multiplicity of